REMARKS/ARGUMENTS

Reconsideration of this Application and entry of the foregoing amendments are requested. Claims 1, 17 and 18, have been amended in view of the Office Action and to better define what the Applicants consider their invention, as fully supported by an enabling disclosure. Claim 2 has been cancelled.

Priority

The Specification was modified in accordance with 37 CFR 1.78(a) (2) by inserting a section entitled "Cross Reference to Related Applications" between the existing title and field of the invention sections referring to the prior application from which the subject application claims priority benefit.

Oath/Declaration

Please find enclosed new oaths or declarations in compliance with 37 CFR 1.67(a).

Claims objections

The typographical error in claim 17 was corrected.

Rejections Under 35 U.S.C. § 112 Second Paragraph

The Examiner rejected claim 18 under 35 U.S.C. § 112, second paragraph for failing to provide proper antecedent to the limitation "polymer". Claim 18 was modified as suggested by the Examiner so that it now recites a "copolymer".

Rejection under 35 U.S.C. § 102

Claims 1-4, 6-8, 10-13 and 20 are rejected as being anticipated by Sirois *et al.* ("Sirois") under 35 U.S.C. § 102(b).

Applicants respectfully traverse the rejection as follows. It is respectfully submitted that Sirois's paper was published on February 4, 1997, less than one year prior to the priority date of the subject application, namely February 3, 1998, the filing date of provisional application no 60/073,554 on which the parent application no. 09/241,561, of which the present application constitute a continuation-in-part, claimed priority. Sirois was authored by three of the named inventors. (Please find enclosed a Declaration under 37 CFR 1.132 signed by the inventors). The claims presently in the case are fully supported in provisional application 60/073,554. This provisional application only differs from the subject application in that it did not contain Example 2 from the subject application. It contained Examples 1 and 3 to 9 which are fully supportive of the rejected claims. It is therefore submitted that Sirois *et al.* does not constitute an applicable reference against the present application.

Claims 1-20 are rejected as being anticipated by Rosenberg *et al.* [WO 93/08845].

The claims have been amended to focus not only on the prevention of restenosis but also on the improved reendothelialization and vascular endothelial function upon local administration of the claimed oligonucleotide. Support for this amendment may be found in the original claims and at Example 2 from p. 27 to p. 34, line 8 of the specification and in figures 13a to 15. Specific support showing the prevention of restenosis effected by the application of a bolus antisense treatment may be found at p. 29, line 16 to p. 31, line 4 and specific support showing vascular reendothelialization and vascular endothelial function effected by the application of a bolus antisense treatment may be found at p. 31, lines 5 to 31.

It is respectfully submitted that '845 merely suggests that antisense could be made against the messengers of PDGF and its vascular receptor. It does not provide any credible evidence that such antisense molecules would effectively prevent restenosis. There are neither enabling methods nor results supporting such a method. It further does not suggest

the use of the claimed oligonucleotide for stimulating reendothelialization or vascular endothelial function. These effects of the claimed oligonucleotide are novel and inventive over the prior art. It is submitted that '845 does not teach or suggest any effect on reendothelization or vascular endothelial function.

Furthermore, the combined effect of the claimed oligonucleotide on the reendothelization and on the endothelial function is not obvious. Endothelium cell proliferation normally involves cellular de-differentiation while endothelium cellular function calls for an arrest of proliferation at the favour of cell differentiation. Both phenomena have been unexpectedly observed by the inventors during local administration of the claimed oligonucleotide in a model of vascular injury.

In view of the foregoing, it is respectfully submitted that the new use is novel and non-obvious over the art of record. Currently, the clinician would not have the knowledge and directions of using the claimed oligonucleotides for enhancing reendothelization and vascular endothelial function. The present invention focuses on the role of the claimed oligonucleotides in reendothelialization and improved vascular endothelial function, which should prevent the access of vasconstrictive molecules to muscle cell tissue and/or which should build an endothelial lining having the competence for producing vasodilating molecules. Reendothelialization which accompanies the prevention of restenosis therefore appears to be a novel and inventive feature of the present invention.

Rejection under 35 U.S.C. § 103(a)

Claims 1-20 are rejected as being unpatentable over Sirois *et al.* and Rosenberg *et al.* [WO 93/08845] in further view of Rosenberg *et al.* [US Patent No. 5,593,974].

Claims 1-20 are further rejected as being unpatentable over Rosenberg *et al.* [US Patent No. 5,593,974] in view of Rosenberg *et al.* [WO 93/08845] and Koyama *et al.*

It is first reiterated that Sirois is not applicable against the present case for the reasons stated above.

As indicated above, the present invention not only demonstrates that PDGFR-β antisense molecules effectively and drastically inhibit restenosis, it also demonstrates that these molecules improve reendothelialization and vascular endothelial function.

The '974 patent does not provide any suggestion of the use of antisense molecules directed against PDGFR-β transcript in the prevention of restenosis. The international publication WO93/08845 does not provide any enabling disclosure or demonstration of such an effect. Koyama *et al.* describe the use of neutralizing antibodies against the receptors to PDGF for inhibiting or preventing restenosis but not the use of antisense molecules for this function. Also, Koyama *et al.* suggest that inhibition of both PDGFR-α and PDGFR-β is needed to achieve a proper inhibition of restenosis. Figure 4b of Koyama, as well the passage of page 685 (the bottom portion of the left column), show that inhibition of PDGFR-β alone with an antibody directed against this particular sub-unit was able to inhibit up to 60% of DNA synthesis. A combined treatment appears to be necessary, since Koyama *et al.* follow by stating that "combined treatment with anti-PDGFR-α and PDGFR-β was able to block > 90% of PDGF mitogenic activity". When reading these segments of Koyama's text, the person skilled in the art would be taught that using anti-molecules directed against PDGFR-β only would not be sufficient to inhibit or prevent restenosis efficiently. Clearly Koyama *et al.* do not teach the present invention. Last but not lease, none of these references teach or suggest any effect on reendothelization or vascular endothelial function. In all aspects, antisense molecules are unexpectedly superior to antibodies.

These references, taken alone or in combination, do not disclose or suggest that the use of antisense molecules directed against PDGFR-β would successfully inhibit or prevent restenosis and would improve reendothelialization and vascular endothelial function.

The rejections of the original claims are believed to have been overcome by the present remarks and the introduction of new claims. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such an action is earnestly solicited.

Authorization is hereby given to charge deposit account no. 17-0055 for any deficiencies or overages in connection with this response.

Respectfully submitted,

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